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# Topography of the chromatic pattern-onset VEP

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The chromatic pattern-onset VEP has been used successfully as a sensitive and objective technique to determine congenital and acquired color vision deficiency. It also has been applied to characterize development, maturation and aging of the chromatic visual pathways. Here we determine the topographic components of the full-field VEP using the multifocal technique. Recordings were made with the VERIS[TM] system that extracts topographic VEPs using a pseudorandom stimulus sequence. Chromatic pattern stimuli were presented in an onset-offset temporal sequence, with colors modulated along different axes in the MBDKL color space. Additional experiments were conducted to verify the S-cone axis for each observer and that our chromatic stimuli were close to isoluminant at different field locations. Our data show reliable and robust chromatic onset VEP responses for multiple retinal areas that conform to pattern-onset full-field VEP waveform characteristics. For stimuli with chromatic contributions, pattern-onsets produced reliable and consistent waveforms whereas for stimuli with large luminance contributions pattern-reversal stimuli were superior. Our method for recording chromatic multifocal pattern-onset VEPs holds promise for clinical application to detect and monitor early retinal and optic nerve changes related to aging and disease.

## Introduction

Visual evoked potential (VEP) recordings are generally accepted as a sensitive and objective test of the integrity of the visual system (e.g. Harding, Odom, Spileers & Spekreijse, 1996). To investigate the focal contribution to the full-field VEP, Baseler et al. (Baseler, Sutter, Klein & Carney, 1994) utilized the multifocal recording technique developed by Sutter (Sutter, 1991; Sutter & Tran, 1992) to record VEPs simultaneously from multiple locations in the visual field. This multifocal technique permits recording and analysis of multiple focal retinal (multifocal electroretinogram) or cortical (multifocal VEP or mfVEP) responses. Several groups have already applied the multifocal technique to record pattern-reversal mfVEPs in normal subjects and in patients with diseases such as glaucoma (Klistorner, Graham, Grigg & Billson, 1998; Klistorner & Graham, 2000; Hood et al, 2000; Hasegawa & Abe, 2001) and amblyopia (Yu, Brown & Edwards, 1998). Detecting response changes by the mfVEP technique prior to visual field losses in glaucoma would provide important information about the onset and progression of the disease (see Goldberg, Graham and Klistorner, 2002).

It is well known that an S-cone pathway is affected early in diseases such as glaucoma, diabetes and retinitis pigmentosa (Sandberg & Berson, 1977; Adams, Rodic, Husted & Stamper, 1982; Greenstein, Hood, Ritch, Steinberger & Carr, 1989). Chromatic cortical responses can be elicited with the pattern-onset VEP using low spatial frequency isoluminant stimuli (Berninger, Arden, Hogg & Frumkes, 1989; Murray, Parry, Carden & Kulikowski, 1987; Rabin, Switkes, Crognale, Schneck & Adams, 1994). Crognale et al. (1993) have shown that chromatic onset VEPs are useful in detecting congenital and acquired color vision deficiency. To be able to determine early and localized abnormalities in the chromatic pathways would be a dramatic improvement in objectively detecting and monitoring retinal and optic nerve diseases. MfVEPs in the chromatic pattern-onset mode have not previously been described in the literature.

The purpose of this paper is to determine the topographic components of the full-field chromatic onset VEP by recording multifocal responses in normal subjects. Using isoluminant stimulus patterns we were

able to record along the tritan (S cone) and L-M axes to confirm the response characteristics described for chromatic onset full-field VEPs (Murray, Parry, Carden & Kulikowski, 1987, Berninger, Arden, Hogg & Frumkes, 1989; Rabin, Switkes, Crognale, Schneck & Adams, 1994). We also obtained responses to isochromatic stimuli that varied in luminance. Additionally, several experiments were conducted to verify isoluminance and S-cone isolation for individual observers.

# General Methods

## Subjects

MfVEPs[1] were obtained from five normal subjects ages 23 to 38 years. The presence of retinal disease and abnormal ocular media in the tested eye were ruled out by ocular examination including visual acuity, slit lamp examination, intraocular pressure and direct and indirect ophthalmoscopy. Color stereo fundus photographs of the macula and optic disc (ETDRS Fields 1 and 2) were evaluated by a retinal specialist using a stereo viewer. The retinae of all subjects were found to have no vascular, retinal, choroidal or optic nerve findings known to disrupt visual function. Intraocular pressure was ≤ 22 mm Hg. All subjects demonstrated a corrected Snellen acuity of ≥ 20/20 in the tested eye, as well as normal color vision when tested with the Neitz anomaloscope, the HRR pseudoisochromatic plates and the Farnsworth F-2 plate. Written informed consent was obtained following the Tenets of Helsinki, and with approval of the Office of Human Research Protection of the University of California, Davis, School of Medicine.

## Equating Perceptual Contrast

Before any mfVEP measurements were made, we first selected stimulus contrasts along the three color dimensions to be tested (tritan, L-M, and luminance axes). Following Switkes and Crognale (1999) we used a psychophysical approach to obtain perceptually equated stimuli for suprathreshold contrast for our experiments.

The stimuli were presented on the same monitor (Sony Trinitron 20") used for the mfVEP experiment driven by a Macintosh G4 computer with an 8 bit IMS Twin Turbo graphics card. The stimulus arrangement was equivalent to the stimulus pattern used by the VERIS™ system except the hexagons were not scaled. For each image, the 19 hexagons were presented simultaneously with a fixation point placed at the center. Illuminant C was chosen as the white point (CIE x,y = 0.310,0.316) and was used as the stimulus background. The test stimuli were modulated from the white point along the three cardinal axes of the MBDKL color space (MacLeod & Boynton, 1979; Derrington, Krauskopf & Lennie, 1984). The chromatic stimulus patterns (tritan and L-M) were

isoluminant across the whole image at 37 cd m$^{-2}$, and the luminance stimulus pattern had a mean luminance value of 37 cd m$^{-2}$.

The experimental software was written in MATLAB (http://www.mathworks.com/) using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). The monitor was calibrated using a Minolta colorimeter (CS 100 Chroma Meter) and procedures set out in Brainard et al. (Brainard, Peli & Robson, 2002). The CIE 1931 color-matching functions and Smith-Pokorny cone fundamentals (Smith & Pokorny, 1975) were used to convert between the measured monitor RGB outputs and cone stimulation.

Using the calibration data, we calculated the maximum distance from the white point in each cone direction using L*a*b* space (an approximately uniform perceptual color space). The least of these values (87.5 DE units) was used as the furthest step for each of the chromatic stimuli. Ten equally spaced step sizes (8.75 DE units) were calculated from the white point to the furthest step (see Figure 1). For the luminance contrast settings, the same chromaticity coordinates as the white point were used, but consisted of 10 equally spaced luminance contrast values above and below the mean luminance value.
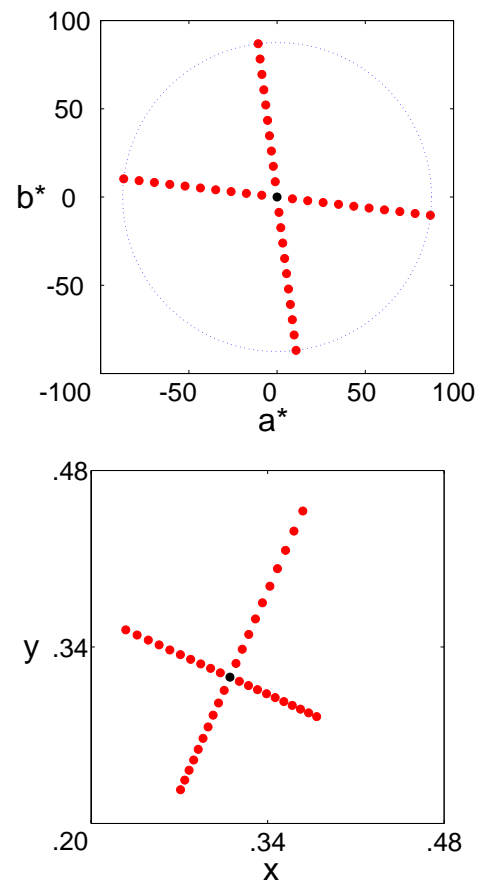


Figure 1. Chromatic axes and step sizes are shown in both CIE a*b* and xy color coordinates. The center point is Illuminant C.
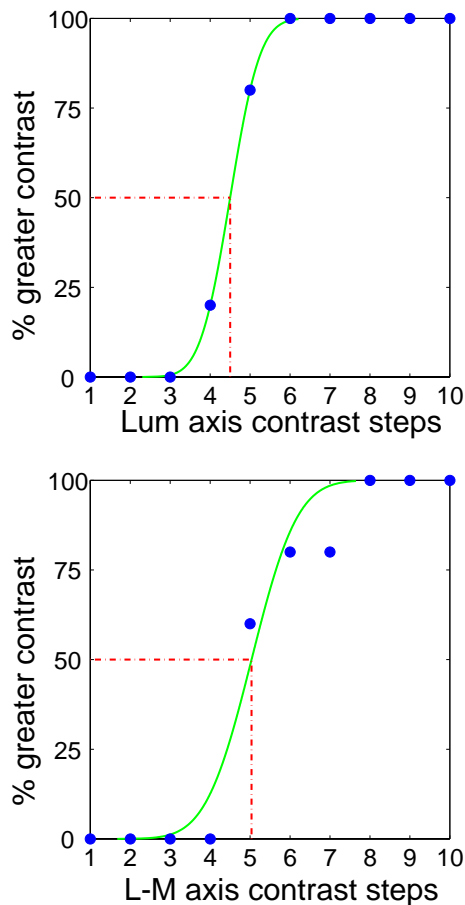
Figure 2. Data are shown (blue dots) for one subject (ABR). Luminance (top panel) and L-M (bottom panel) stimuli of varying contrasts were compared to the tritan standard. A psychometric function was fitted to the data (green curves) to estimate the PSE (red dashed lines).

An S-cone contrast setting was chosen as the standard and the L-M and luminance stimuli were tested against it. This S-cone setting was chosen in a pilot experiment so that there were approximately equal step sizes above and below this setting for the other two dimensions. A 2AFC constant stimulus procedure was used. For each stimulus pair, the standard was shown against either an L-M or luminance stimulus. The presentation order was randomized, as was the order of the contrast step-size of the test stimuli. Each stimulus pair was presented sequentially and the observer indicated which interval contained the highest contrast by pressing either '1' or '2' on a number keyboard. Presentation time was 1 s for each stimulus pattern, with a 0.2 s interval between the pair. Both sets of stimuli (L-M and luminance) were tested in the same experiment monocularly. Each contrast step was tested five times requiring a total of 100 trials (2 dimensions x 10 step sizes x 5 presentations).

The data were fitted with a cumulative normal psychometric function and the point of subjective equality (PSE) was the contrast at the 50% point (see Figure 2 for example). The values at these points were

converted to RGB input values for the VERIS™ system using the calibration data. A separate set of values was calculated for each subject. The cone values and Michelson contrasts are shown in Table 1. Note that the values are similar across subjects.

Table 1. Perceptually Equated Cone Stimulation Values and Michelson Contrasts.

|     |   | S+ | S- | Cont. | L+M- | L-M+ | Cont. | Lum+ | Lum- | Cont. |
|-----|---|--------|--------|------|--------|--------|------|--------|--------|------|
| ABR | L | 0.0762 | 0.0757 | 0% | 0.0790 | 0.0729 | 4% | 0.0813 | 0.0706 | 7% |
|     | M | 0.0645 | 0.0642 | 0% | 0.0593 | 0.0692 | -8% | 0.0689 | 0.0598 | 7% |
|     | S | 0.0730 | 0.0288 | 43% | 0.0490 | 0.0490 | 0% | 0.0524 | 0.0455 | 7% |
| CIS | L | 0.0762 | 0.0757 | 0% | 0.0790 | 0.0730 | 4% | 0.0812 | 0.0707 | 7% |
|     | M | 0.0645 | 0.0642 | 0% | 0.0594 | 0.0691 | -8% | 0.0688 | 0.0599 | 7% |
|     | S | 0.0730 | 0.0288 | 43% | 0.0490 | 0.0490 | 0% | 0.0524 | 0.0456 | 7% |
| CG  | L | 0.0762 | 0.0757 | 0% | 0.0791 | 0.0728 | 4% | 0.0814 | 0.0705 | 7% |
|     | M | 0.0645 | 0.0642 | 0% | 0.0592 | 0.0693 | -8% | 0.0690 | 0.0597 | 7% |
|     | S | 0.0730 | 0.0288 | 43% | 0.0490 | 0.0490 | 0% | 0.0525 | 0.0454 | 7% |
| PBD | L | 0.0762 | 0.0757 | 0% | 0.0790 | 0.0729 | 4% | 0.0812 | 0.0707 | 7% |
|     | M | 0.0645 | 0.0642 | 0% | 0.0594 | 0.0692 | -8% | 0.0688 | 0.0599 | 7% |
|     | S | 0.0730 | 0.0288 | 43% | 0.0490 | 0.0490 | 0% | 0.0524 | 0.0456 | 7% |
| SMG | L | 0.0762 | 0.0757 | 0% | 0.0785 | 0.0734 | 3% | 0.0805 | 0.0714 | 6% |
|     | M | 0.0645 | 0.0642 | 0% | 0.0601 | 0.0685 | -6% | 0.0682 | 0.0605 | 6% |
|     | S | 0.0730 | 0.0288 | 43% | 0.0490 | 0.0490 | 0% | 0.0519 | 0.0461 | 6% |

Values for each of the five subjects are listed. Note that the S-cone contrast was fixed and the contrasts along the other two axes (L-M and luminance) were equated to it psychophysically.

## MfVEP Stimulus and Procedure

The stimulus array was produced and displayed on a CRT using the VERIS™ 4.8 multifocal system. This system has proven to be a useful tool for multifocal recording particularly in clinical environments (see http://www.cephalon.dk/ for further information). It is also useful for experimental work but for our purposes there are two limitations worth noting. First, the choice of stimulus patterns is currently limited. The system does offer a cortically scaled pattern (dartboard) but it contains many edges (especially in the central area) that produce a substantial level of high spatial frequency components. For our purposes it was more important to reduce high spatial frequency components and the 'triangle pattern' was therefore chosen. Note that further VERIS™ software will provide an option to import customized stimulus patterns (Erich Sutter, personal communication, December 2002).

Second, the system includes a customized graphics card that currently allows only 101 values per gun. Although this resolution is relatively low, a control experiment (see next section) suggests that the resolution level was sufficient for our purposes.

The pattern we used contained 19 scaled hexagons (although not cortically scaled) and each hexagon consisted of 24 triangles (see Figure 3 and 4). The stimuli

were viewed from a distance of 60 cm and had a retinal subtense of 14 degrees in radius with a central hexagon over 2.5 degrees, a second ring (containing 6 hexagons) from 2.5 – 8 degrees and an outermost ring (12 hexagons) from 8 – 14 degrees. The stimulus was presented on a 20" SONY Trinitron color monitor (frame rate 75 Hz).
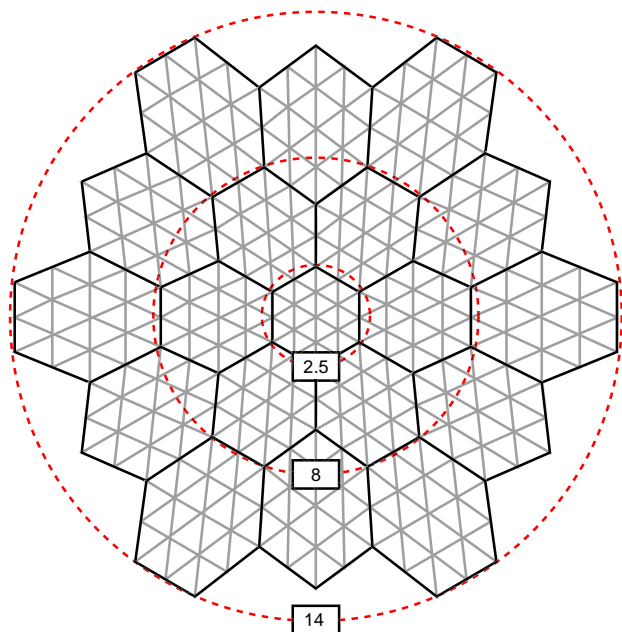


Figure 3. The VERIS™ triangle pattern is shown. The red rings are superimposed to illustrate the extent of retinal stimulation (in degrees radius).



Figure 4. This movie shows the L-M stimulus pattern used in Experiment 1.

MfVEPs were recorded monocularly (same eye that was tested in the color contrast experiment) with silver-silver chloride electrodes placed at $O_z$ (active), $F_z$ (reference) and $C_z$ (ground) following the International 10/20 system (Harding, Odom, Spileers & Spekreijse, 1996). The scalp-electrode impedance was ≤ 6 kΩ. The subjects were instructed to fixate the target (black cross) in an alert condition. Each recording was divided into 32 segments, each 51.18 sec long with a resulting total recording time of 27 min 18 sec. The continuously recorded mfVEP was amplified ($10^5$), band-pass filtered at 1-100 Hz (GRASS preamplifier CP511) and sampled at 1200 Hz (every 0.83 ms). The m-sequence was set to $2^{12}$– 1. First-order kernel responses were extracted and analyzed using VERIS™ 4.8.

The nomenclature ($C_I/C_{II}/C_{III}$) recommended by the ISCEV Standard for Visual Evoked Potentials 1995 (Harding et al., 1996) was used for the response analysis (see Figure 5). In our analysis we paid particular attention to $C_I$ and $C_{II}$ because typically $C_I$ is larger for isochromatic luminance modulation and $C_{II}$ is larger for isoluminant chromatic modulation. In our experiment, $C_{III}$ covaried with $C_{II}$ and therefore did not provide any further information. Thus, we have restricted our discussion to $C_I$ and $C_{II}$.
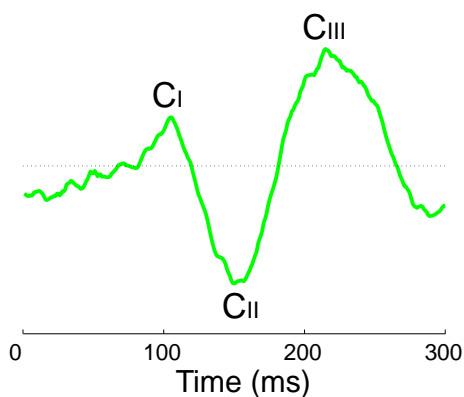


Figure 5. The three main components of a pattern-onset VEP waveform are shown. (This waveform is a response to one of our experimental conditions that varied in both luminance and chromaticity.)

## Verification of Tritan Axis Stimulation

Before proceeding with the mfVEP recordings, we wanted to verify that our stimuli produced the desired pathway stimulation. There are a number of possible reasons why our stimulus patterns might not do this. As mentioned above, the VERIS™ system has relatively low color resolution (101 values per gun). Also, the cone stimulation values we used are based on Smith-Pokorny's (1975) cone fundamentals while the actual values for individual observers with normal color vision will vary slightly. Finally, the calibration procedure assumes monitor spatial homogeneity and phosphor independence and small violations may also introduce some degree of error.

We tested whether our tritan stimulus matched the tritan axis for each of the observers used in the main experiment with a transient tritanopia paradigm (Mollon & Polden, 1977; Crognale et al., 1995). We asked observers to rate the stimulus contrast before and after adaptation to a bright 580 nm field. Following the extinction of this adapting field, thresholds for lights detected by a short-wavelength cone pathway are elevated due to polarization of a cone-opponent site of adaptation. If the stimulus pattern were sufficiently close to the observer's tritan axis, the perceived contrast of the pattern should be reduced after adaptation.

Subjects viewed, with the same eye to be tested in the mfVEP experiment, a 580 nm, 16° diameter, 10.5 log quanta sec$^{-1}$ deg$^{-2}$ adapting background in Maxwellian view for 30 sec. They then immediately inspected one of the three test patterns used in the mfVEP Experiment. Ratings of stimulus contrast were made for the adapted and unadapted eyes before and after adaptation.

As expected, there was no intra-ocular transfer of adaptation as evidenced by similar ratings before and after adaptation in the unadapted eye. The tritan stimulus was essentially invisible to all subjects following adaptation, while the L-M axis and luminance stimulus were essentially unchanged, if not slightly enhanced in their perceived contrast. Table 2 shows the individual ratings for each stimulus pattern. This experiment demonstrates that in all subjects the tritan stimulus used for the mfVEP recording was effective at isolating an S-cone pathway.

Table 2. Perceived Contrast Before and After Transient Tritanopia.

| Subject | Pattern | Before adapt | | After adapt | |
|---------|---------|-------|------|-------|------|
| | | Right | Left | Right | Left |
| **ABR** | Tritan | 10 | 10 | 10 | **0** |
| | L-M | 10 | 9 | 10 | 10 |
| | Luminance | 10 | 9 | 10 | 13 |
| **CIS** | Tritan | 10 | 9 | 9 | **0** |
| | L-M | 10 | 10 | 10 | 9 |
| | Luminance | 10 | 10 | 10 | 12 |
| **CG** | Tritan | 10 | 10 | 10 | **0.5** |
| | L-M | 10 | 10 | 10 | 10 |
| | Luminance | 10 | 10 | 10 | 11 |
| **PBD** | Tritan | 10 | 10 | 10 | **0** |
| | L-M | 10 | 10 | 10 | 10 |
| | Luminance | 10 | 10 | 10 | 10 |
| **SMG** | Tritan | 10 | 10 | 10 | **0** |
| | L-M | 10 | 9 | 10 | 9 |
| | Luminance | 10 | 10 | 10 | 10 |

After adaptation, there is essentially no perceived tritan contrast (highlighted in blue).

# Experiment 1: Chromatic Pattern-Onset mfVEP

MfVEP responses were recorded when subjects were presented with perceptually equated contrast pattern-onset stimuli. Contrast was modulated along three axes (luminance, L-M, and tritan) as described in detail above.

## Results and Discussion

Figure 6 shows mfVEP waveforms for two subjects (CG and CIS) and the average for all 5 subjects: the S axis responses (blue) are superimposed on either the L-M axis responses (red; left panel) or the luminance responses (black; right panel). For both chromatic and luminance modulation, the second response component (C$_{II}$) is faster and smaller with increasing eccentricity. The responses are largely dominated by the fovea, which is demonstrated by robust waveforms from the central area. Peripheral responses suggest a lower signal-to-noise ratio with smaller response amplitudes than central responses.[2] In the majority of the recordings, waveforms in the superior and inferior field do not demonstrate an obvious change in polarity as described for the pattern-reversal mfVEP (e.g. Baseler, Sutter, Klein & Carney, 1994; Baseler & Sutter, 1997; Yu & Brown, 1997). The use of single-channel recording and the electrode positioning (see Klistorner, Graham, Grigg & Billson, 1998 and Hood, Zhang, Hong & Chen, 2002) might contribute to the failure to observe polarity changes in our records.

*Tritan responses:* In agreement with previous studies on chromatic pattern-onset VEPs (e.g. Rabin et al., 1994), the responses along the S axis are characterized by a negativity (C$_{II}$) after 100 to 160 ms. In all subjects the slowest C$_{II}$ latencies were found in the central/foveal response (subjects: CG: 148 ms; CIS: 132 ms; ABR: 134 ms; SMG: 129 ms; PBD: 152 ms) compared to the other 18 areas tested. Most of the responses did not exhibit a well-formed positive (C$_I$) component.

*L-M axis responses:* The responses to L-M modulation are similar in magnitude and shape to the tritan responses. C$_{II}$ latencies for the L-M responses were found to be slightly faster than the tritan responses as demonstrated in the upper panel in Figure 6 and as reported previously for the full-field VEP (e.g. Rabin et al., 1994).

*Luminance responses:* Responses to luminance modulation are characterized by smaller C$_{II}$ components, which are less pronounced in the periphery compared to chromatic responses. More often than in the chromatic responses there are well-demarcated C$_I$ luminance response components. Based on previous recordings of low spatial frequency pattern-onset VEPs (Murray et al., 1987; Rabin et al., 1994), one might expect smaller responses to luminance onset pattern stimuli. We assume that the present luminance responses are larger due to

additional contributions from mechanisms sensitive to high spatial frequencies in our patterns. We investigate this issue further in Experiment 3.

## Experiment 2: Chromatic Pattern-Reversal mfVEP

Full-field VEP studies have shown that for low spatial frequency stimuli, pattern-onset stimulation is superior to the pattern-reversal presentation for recording robust and reliable isoluminant chromatic responses (Murray et al., 1987; Berninger et al., 1989; Rabin et al., 1994). We ask whether this full-field response characteristic is valid for the multifocal stimulation technique and repeated the previous stimulation conditions but with the reversal presentation.

## Additional Methods

We recorded the tritan pattern-reversal mfVEP for one of the subjects (PBD) with the same stimulus pattern, color settings and data acquisition as we used for the pattern-onset stimulation. To accomplish the reversal stimulation, one frame per m-step was used. The m-sequence was set to $2^{12}$–1. The recording was divided into 2 segments, each 27.30 sec long with a resulting total recording time of 55 sec per run. The surround was set to Illuminant C. Responses for the first slice of the second-order kernel, which represent the interaction between two consecutive frames of the monitor (Baseler et al., 1994) were extracted and analyzed using VERIS™ 4.8.

To directly compare the pattern-reversal and the pattern-onset mfVEP responses, we repeated the pattern-onset test in the same session and with the same electrode position. The onset stimulus used 6 'on' frames and 6
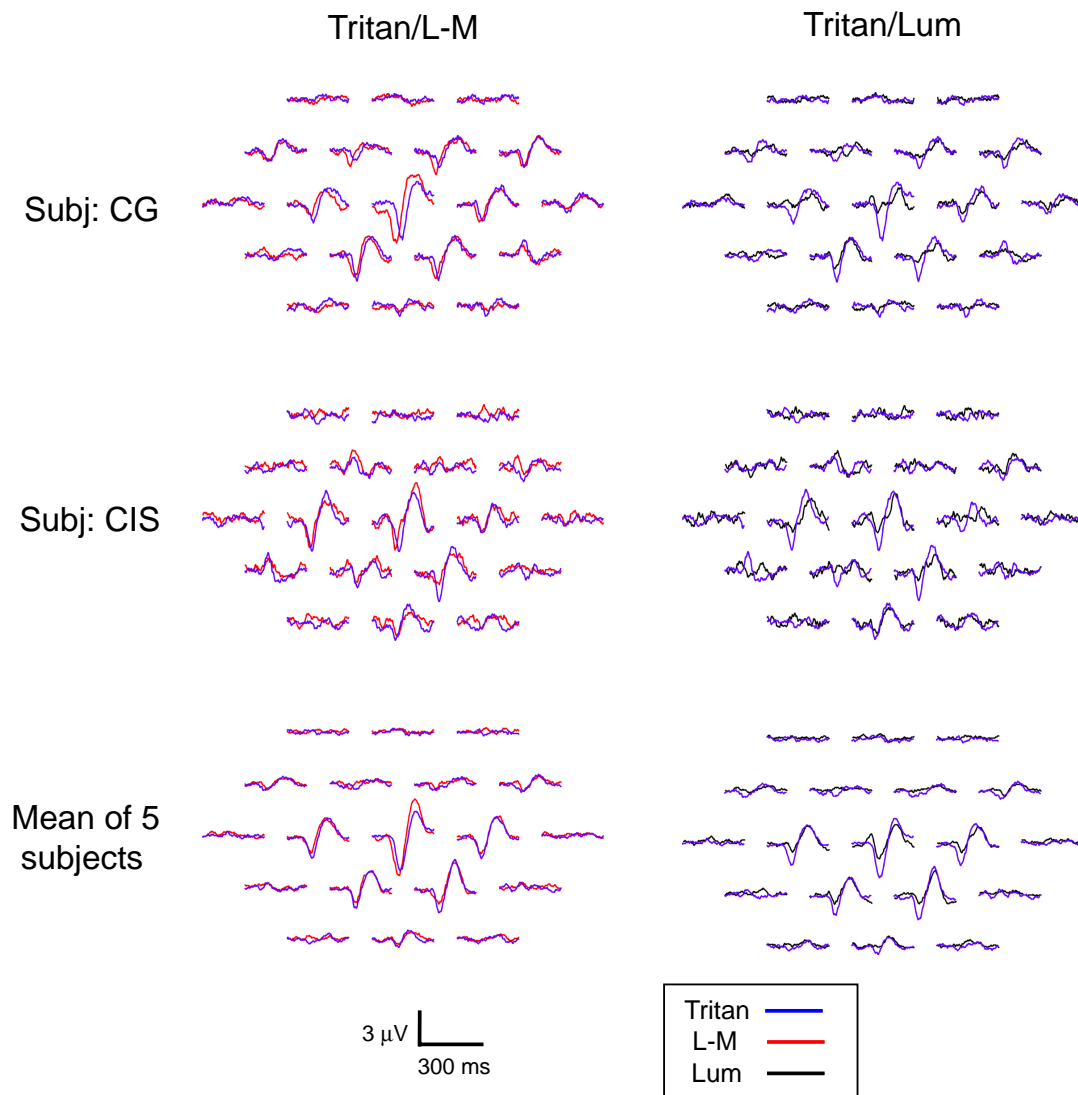


Figure 6. Response waveforms are shown for two subjects and for the mean of all 5 subjects. The waveforms in the left column are for tritan (blue) and L-M (red) responses. The right column shows the tritan (blue) and luminance (black) responses.

'off' frames for each m-sequence step. Pilot recordings using the temporal settings of 6 chromatic or luminance stimulus frames as 'on' and 6 blank frames as 'off' did not differ from the 6 'on'/24 'off' in their waveform characteristics. The recording was divided into 16 segments, each 41.23 sec long with a resulting total recording time of 10 min 36 sec per run. Blank frames and the surround were set to Illuminant C.

A mean luminance value of 30 cd · m$^{-2}$ was used for all conditions in this control experiment.[3] Two runs of both the reversal and onset conditions were performed in the same session so that a two-run signal to noise ratio (2rSNR) analysis could be performed (Zhang, Hood, Chen, Hong, 2002). The responses from 45 – 300 ms were used in the analysis (the responses in the first 45 ms of the recordings are due mainly to cortical noise).

## Results and Discussion

In Figure 7 individual waveforms for the pattern-onset mfVEP (top panel) and pattern-reversal mfVEP (bottom panel) are shown. In contrast to the tritan pattern-onset waveforms, the pattern-reversal responses are less distinct and smaller in their amplitude. The pattern-reversal responses exhibit a small negativity at around 100 to 120 ms having decreasing amplitudes with increasing retinal eccentricity. The rather typical sharp negativity ($C_{II}$), which is evident for the tritan onset responses, is less distinct for the pattern-reversal presentation. These findings parallel full-field VEP responses.

The 2rSNR analysis results are shown above each set of responses. Values of zero indicate no signal, and values above 1 have a high probability of a signal being present (Zhang et al., 2002). The 2rSNR values for the onset responses are significantly greater than for the reversal responses (*t*-test, p < .01).

The onset stimulus used 12 frames for each step of the m-sequence, whereas the reversal stimulus used only 1 frame per step. Therefore the recordings for the onset conditions are twelve times longer. The important consideration was to equate the m-sequence for both types of stimulus presentation so that the sampling rates were identical.

The results confirm that the pattern-onset stimulation is better for studying chromatic mfVEP responses for both the full-field (Murray et al., 1987; Rabin et al., 1994) and localized contributions.

## Experiment 3: Control for High Spatial Frequency Contributions

As mentioned previously, the choice of stimulus patterns available with the VERIS$^{TM}$ system is limited and the pattern we chose contained sharply defined edges that introduced undesirable high-spatial frequency
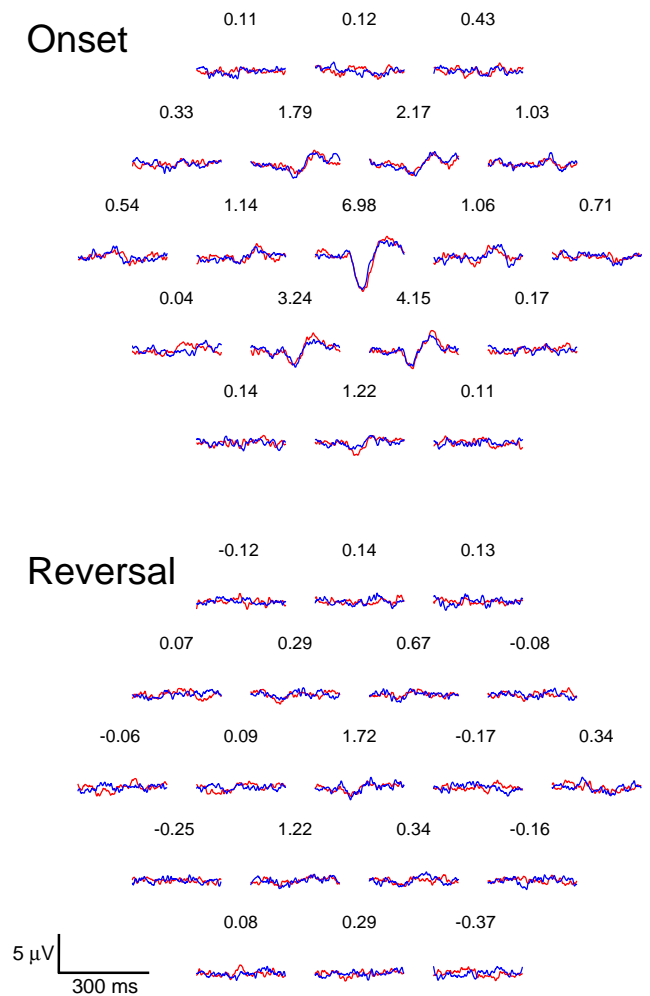


Figure 7. Tritan responses are shown for both pattern-onset stimuli (top panel) and pattern-reversal stimuli (bottom panel). The red and blue traces show the responses from two different runs in the same session. The 2rSNR values are shown above each set of responses.

components. To help determine the degree to which these components affected our results, we conducted an additional experiment with a lens placed in front of the observer's eye to blur the stimulus.

## Additional Methods

One of the subject's (CG) mfVEP recordings were repeated for the luminance and the tritan stimulus on the same eye tested as in the original experiment. The stimulus was blurred with a + 3.0 D trial lens,[4] which would be expected to shift the high spatial frequency cut-off to $\leq$ 6 cycles per degree (Westheimer, 1964).

## Results and Discussion

In Figure 8 waveforms are superposed for 'in focus' (red) and 'blurred' (blue) recordings with the tritan stimulus (top panel) and the luminance stimulus (bottom

panel). Responses to both stimulus patterns are affected, however, the luminance responses are affected to a larger degree. The $C_I$ component seems to be less affected than the $C_{II}$ and $C_{III}$ components when the stimulus is blurred. For the luminance response, the $C_{II}$ and $C_{III}$ components are almost extinguished under the blur condition. It is likely that for stimuli with even lower spatial frequencies, the luminance response would be extinguished. For the S stimulus the responses still exhibit well-demarcated $C_{II}$ and $C_{III}$ components, which are smaller in amplitude and slower in peak latency than in the 'in focus' response. Overall, the sharp negativity ($C_{II}$) of our 'in focus' luminance stimulus appears to depend on the presence of high spatial frequency components. The tritan responses are preserved with induced blur. This agrees with previous reports using low spatial frequency stimuli where tritan responses are much more pronounced than luminance responses (e.g. Rabin et al., 1994).
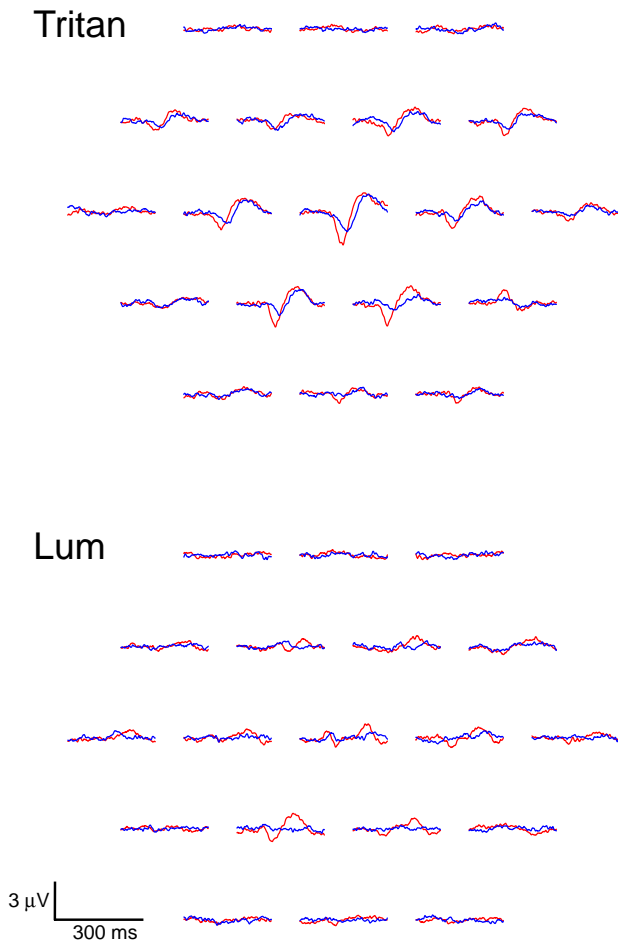


Figure 8. The waveforms for in-focus (red traces) versus blurred (blue traces) stimuli are shown for tritan responses (top panel) and luminance responses (bottom panel).

# Experiment 4: Control for Isoluminance

Previous research has shown that the $C_I$ component is maximized for isochromatic luminance modulation and $C_{II}$ for isoluminant chromatic modulation (e.g. Rabin et al., 1994). The purpose of this experiment was to determine which components are generated by chromatic versus luminance pathways in the mfVEP by varying the luminance and chromatic components of those stimuli. To do this, the original chromatic axes were tilted into the luminance plane by varying amounts to change the relative chromatic and luminance modulation of the stimuli. MfVEPs were recorded with these new stimuli.

## Additional Methods

Eight new test axes were created using a combination of the chromatic and luminance axes used in the *General Methods/Perceptual Contrast Experiment*. The contribution of each component was based on the angle of tilt. For example, for a +30 degree tilt, the axis consisted of 50% of the original luminance axis and 88.6 % of the original chromatic axis (see Figure 9). The two original chromatic axes were tilted into the luminance plane using four different angles (+/- 30 degs, +/- 60 degs). Switkes and Crognale (1999) showed that the PSE for one chromatic axis could predict the PSE on another. We therefore estimated the new PSEs for the new axes using the results from the perceptual contrast experiment (see General Methods section).
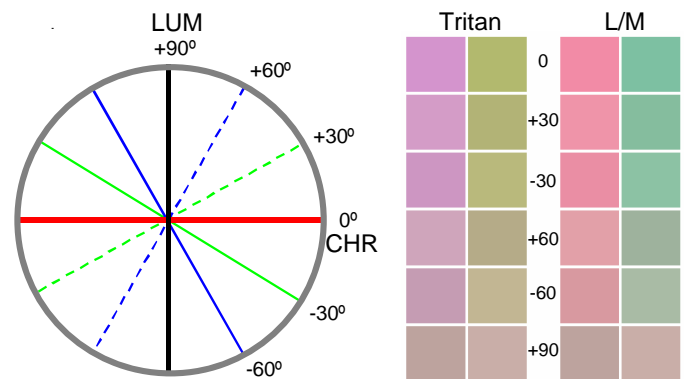


Figure 9. The tilted axes are illustrated on the left. The stimulus contrasts are illustrated on the right. (The colors are approximations only. In the experiments, all stimuli were presented on a carefully calibrated monitor.)

A mean luminance value of 30 cd · m$^{-2}$ was used for this set of experiments. To avoid inter-session variability, the original three conditions were repeated together with the eight new conditions in one test session. The onset stimulus used 6 'on' frames and 6 'off' frames for each m-sequence step. The m-sequence was set to $2^{12}$–1 and the

first-order kernel responses were extracted and analyzed using VERIS™ 4.8. Blank frames and the surround were set to Illuminant C. All 11 tests were recorded on three of the original five subjects (CG, CIS, PBD) within one test session.

## Results and Discussion

If the chromatic stimuli are close to isoluminance, the results from the tilted axes should fall between the chromatic and luminance responses. Figure 10 shows the responses from the central area for the tritan, luminance and tilted axis responses for one subject. Note that the tilted responses do indeed fall between the chromatic and luminance responses and that the +/- 30 degree responses are closer to the chromatic response and the +/- 60 degree responses are closer to the luminance response. This provides compelling evidence that the chromatic axis is close to isoluminant. To summarize the responses, we measured the CII response density using the scalar product method (see Sutter 1992) for each of the waveforms. $C_{II}$ was chosen because it is large for chromatic modulation and low for luminance modulation. Figure 11 shows the $C_{II}$ response densities for the tritan axis for the central region for one observer (CG).



Figure 10. The waveform responses to the tritan, luminance and tilted axes are shown for the central region for one subject. Note that the responses to the tilted axes are generally between the tritan and luminance responses suggesting that the chromatic stimuli are close to isoluminant.

An inverted-U shape suggests that the chromatic stimuli were close to isoluminant (recall that the $C_{II}$ component largely reflects inputs from chromatic pathways). This inverted-U shape was found in the central, parafoveal and some of the outer regions (see Figure 12). Some of the outer regions had weak responses but no location showed a luminance response

contribution to the $C_{II}$ component. This indicates that a pattern that is isoluminant for the central region is close to isoluminant in the periphery. Luminance artifacts due to retinal inhomogeneity do not seem to have much of an impact on the peripheral results using the present procedure. The tritan responses are shown because this axis is particularly vulnerable to violations of isoluminance (due to retinal inhomogeneity of macular pigment density). The results for the L-M axis were similar.
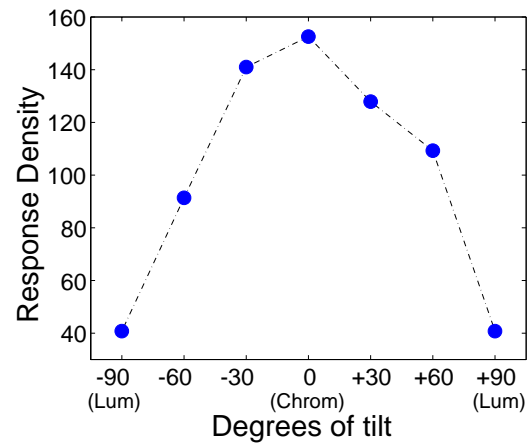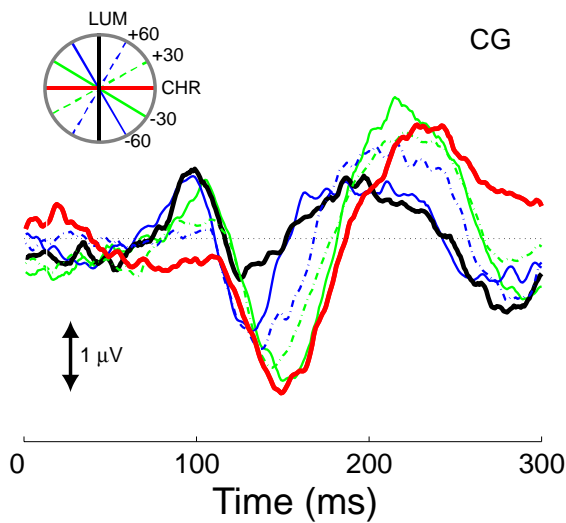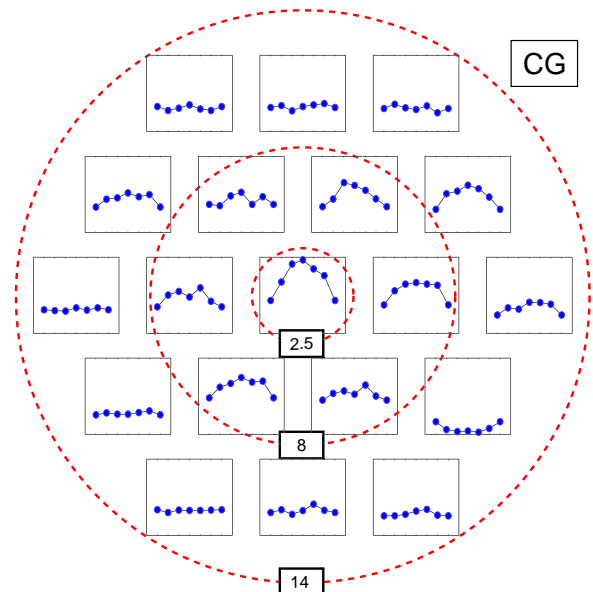


Figure 11. These are the $C_{II}$ response densities for the waveforms shown in Figure 10. The inverted-U shape indicates that the chromatic stimuli are isoluminant.



Figure 12. These plots show the $C_{II}$ response densities for one subject for the tritan, luminance and tilted axes. Each subplot is in the same format as Figure 11. The inverted-U shape was found in the central region, middle regions and some outer regions. The red rings illustrate the radius (in degrees) of the stimulated retinal areas..

## Conclusions

The VERIS™ system is a useful tool for recording multifocal responses. It has, however, been designed mainly for clinical applications and the software presently available has some limitations for experimental use (in particular, relatively low color resolution and a restricted choice of stimulus patterns). Despite these limitations, we were successfully able to record chromatic onset mfVEPs at multiple field locations. In agreement with previous research (Murray et al., 1987; Berninger et al., 1989; Rabin et al., 1994) we found that chromatic responses are much larger using the pattern-onset rather than the pattern-reversal mode of presentation. The chromatic onset responses are similar in their waveform and latency to full-field responses reported previously (Murray et al., 1987; Rabin et al., 1994). The responses obtained from the two chromatic axes we used (tritan and L-M) are mainly dominated by the fovea. Responses in the peripheral field are smaller and have a lower signal-to-noise ratio.

With the transient tritanopia experiment we have demonstrated that in all subjects the stimulus we used for mfVEP recording essentially stimulates only an S-cone pathway for the entire test field. Further, the tilted axes experiment showed that the $C_{II}$ response amplitude peaked at the isoluminant point and was minimal at the luminance point in the central and in more than 50% of the peripheral responses extending 14 degrees in radius. No obvious waveform polarity differences were observed between the superior and inferior areas of the field. This is likely to be due to the electrode placement and the one channel recording technique (Klistomer et al, 1998; Hood, Zhang, Hong, & Chen, 2002).

The validity of large field chromatic VEPs and mfVEPs depends on minimal disruption of isoluminance due to retinal inhomogeneity (Kulikowski, Robson & McKeefry, 1996; Switkes, Crognale, Rabin, Schneck & Adams, 1996). Several authors (e.g. Rabin et al., 1994; Porciatti & Sartucci, 1999) have shown that for full-field isoluminant stimuli intentional luminance contamination does not appreciably alter the chromatic response. Our results, demonstrating very small peripheral luminance response at low spatial frequencies (see Figure 6), support this observation. Therefore, luminance artifacts in larger field sizes would not contribute appreciably to the overall response.

Luminance mfVEPs show reliable response contributions from all field locations for a stimulated area up to 52 degrees (Klistorner & Graham, 2000). Hood, Yu, Zhang, Albrecht, Jaegle, & Sharpe (2002) were able to isolate responses from an L-M-cone pathway in all field locations subtending 22.2 degree in radius using the pattern-reversal mode. We do not believe that the different modes of stimulus presentation (pattern-reversal versus onset) is the basis for low peripheral responses in our recordings.

It has been shown that isoluminant VEPs for tritan and L-M axes are tuned to low spatial frequencies (Rabin et al., 1994). The negative response ($C_{II}$) decreases in amplitude and increases in latency as spatial frequency moves above about 3 cycles per degree (cpd). The small peripheral responses to chromatic reversal stimuli might be due to high spatial frequency attenuation of chromatic responses (Murray et al., 1987; Rabin et al., 1994). The optimal stimuli to elicit robust chromatic pattern-onset full-field VEPs are sinusoidal gratings with spatial frequencies 0.5 – 2 cpd depending on the chromatic axis (Murray et al., 1987; Rabin et al., 1994; Porciatti & Sartucci, 1999). It would be preferable to use sinusoidal gratings (Gabor patches) to record chromatic onset mfVEPs, but this type of stimulus is currently not available with the VERIS™ system. In addition, the scaling of the stimulus pattern we used produced smaller peripheral responses and should be re-examined in view of the dependence of cortical signals on retinal eccentricity of the stimulus (Celesia & Meredith, 1982; Yiannikas & Walsh, 1983) due to cortical magnification (Rovamo & Virsu, 1979; Horton & Hoyt, 1991). Further studies are needed to optimize the scaling and spatial frequency for each chromatic axis.

In conclusion, mfVEPs to chromatic onset patterns display characteristic features shown for full-field recording. The validity of the multifocal approach was verified by experiments demonstrating S-cone isolation and isoluminance at different field locations. Stimulation with pattern-onsets produced reliable and consistent waveforms for chromatic modulation, but pattern-reversal stimuli were superior for luminance modulation. Further refinement of the methods introduced here for recording chromatic multifocal pattern-onset VEPs have potential application for detecting early changes in the retina and optic nerve associated with aging and disease.

## Acknowledgments

## Footnotes

1. In the following sections we use the term mfVEP to refer to the pattern-onset mode unless otherwise stated.
2. Further tests of each condition would be needed to conduct a formal signal-to-noise analysis (e.g. Zhang et al.,

2002). We believe this will be meaningful only after the stimulus and recording techniques are optimized.

3. When creating the tilted axes stimuli at a luminance value of 37 cd · m$^{-2}$, we noticed that the VERIS$^{TM}$ system automatically makes slight changes to some RGB values after the manual input. This apparently happens so that the values comply with the luminance calibration tables implemented internally by the VERIS$^{TM}$ system. We found that the RGB values remained largely unchanged at the 30 cd · m$^{-2}$ level. These changes had no significant effect on the original three axes used in Experiment 1. In addition, the transient tritanopia control experiment also suggests that the stimuli in Experiment 1 were sufficiently close to the tritan and L-M axes.

4. The magnification induced by the lens for this recording condition was 1.13 and had only a negligible impact on the retinal area stimulated.

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